ZALTRAP- ziv-aflibercept solution, concentrate
sanofi-aventis U.S. LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZALTRAP safely and effectively. See full prescribing information for ZALTRAP.

ZALTRAP® (ziv-aflibercept)
Injection for Intravenous Infusion
Initial U.S. Approval: 2012

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING

See full prescribing information for complete boxed warning.

- **Hemorrhage: Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in patients who have received ZALTRAP. Do not administer ZALTRAP to patients with severe hemorrhage. (5.1)**
- **Gastrointestinal Perforation: Discontinue ZALTRAP therapy in patients who experience GI perforation. (5.2)**
- **Compromised Wound Healing: Discontinue ZALTRAP in patients with compromised wound healing. Suspend ZALTRAP for at least 4 weeks prior to elective surgery, and do not resume for at least 4 weeks following major surgery and until the surgical wound is fully healed. (5.3)**

INDICATIONS AND USAGE

ZALTRAP, in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen. (1)

DOSAGE AND ADMINISTRATION

- 4 mg/kg as an intravenous infusion over 1 hour every 2 weeks. (2.1, 2.4)
- Do not administer as an intravenous (IV) push or bolus. (2.4)

DOSAGE FORMS AND STRENGTHS

- Single-use vials: 100 mg/4 mL (25 mg/mL), 200 mg/8 mL (25 mg/mL) (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Adverse reactions, sometimes severe and life-threatening or fatal, have been seen in clinical trials with ZALTRAP, including:

- Fistula Formation: Discontinue ZALTRAP if fistula occurs. (2.2, 5.4)
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend ZALTRAP if hypertension is not controlled. Discontinue ZALTRAP if hypertensive crisis develops. (2.2, 5.5)
- Arterial Thromboembolic Events (ATE) (e.g., transient ischemic attacks, cerebrovascular accident, angina pectoris): Discontinue ZALTRAP if ATE develops. (5.6)
- Proteinuria: Monitor urine protein. Suspend ZALTRAP when proteinuria ≥ 2 grams per 24 hours. Discontinue ZALTRAP if nephrotic syndrome or thrombotic microangiopathy (TMA) develops. (2.2, 5.7)
- Neutropenia and Neutropenic Complications: Delay administration of ZALTRAP/FOLFIRI until neutrophil count is ≥ 1.5 $\times 10^9$/L. (5.8)
- Diarrhea and Dehydration: Incidence of severe diarrhea and dehydration is increased. Monitor elderly patients more closely. (5.9, 8.5)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue ZALTRAP. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (all grades, ≥20% incidence and at least 2% greater incidence for the ZALTRAP/FOLFIRI regimen) were leukopenia, diarrhea, neutropenia, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, ZALTRAP may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into account the importance of the drug to the mother. (8.3)
- Females and Males of Reproductive Potential: Use highly effective contraception during and up to a minimum of 3 months after the last dose (8.8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING

Hemorrhage: Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in the patients who have received ZALTRAP in combination with FOLFIRI. Monitor patients for signs and symptoms of GI bleeding and other severe bleeding. Do not administer ZALTRAP to patients with severe hemorrhage [*see Dosage and Administration (2.2), Warnings and Precautions (5.1)*].

Gastrointestinal Perforation: Gastrointestinal (GI) perforation including fatal GI perforation can occur in patients receiving ZALTRAP. Discontinue ZALTRAP therapy in patients who experience GI perforation [*see Dosage and Administration (2.2), Warnings and Precautions (5.2)*].

Compromised Wound Healing: Severe compromised wound healing can occur in patients receiving ZALTRAP/FOLFIRI. Discontinue ZALTRAP in patients with compromised wound healing. Suspend ZALTRAP for at least 4 weeks prior to elective surgery, and do not resume ZALTRAP for at least 4 weeks following major surgery and until the surgical wound is fully healed [*see Dosage and Administration (2.2), Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

ZALTRAP, in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

Administer ZALTRAP 4 mg per kg as an intravenous (IV) infusion over 1 hour every two weeks. Administer ZALTRAP prior to any component of the FOLFIRI regimen on the day of treatment [*see Clinical Studies (14)*].

Continue ZALTRAP until disease progression or unacceptable toxicity.

2.2 Dose Modification/Treatment Delay Recommendations

Discontinue ZALTRAP for:

- Severe hemorrhage [*see Boxed Warning, Warnings and Precautions (5.1)*]

- Gastrointestinal perforation [*see Boxed Warning, Warnings and Precautions (5.2)*]
- Compromised wound healing [*see Boxed Warning, Warnings and Precautions (5.3)*]
- Fistula formation [*see Warnings and Precautions (5.4)*]
- Hypertensive crisis or hypertensive encephalopathy [*see Warnings and Precautions (5.5)*]
- Arterial thromboembolic events [*see Warnings and Precautions (5.6)*]
- Nephrotic syndrome or thrombotic microangiopathy (TMA) [*see Warnings and Precautions (5.7)*]
- Reversible posterior leukoencephalopathy syndrome (RPLS) [*see Warnings and Precautions (5.10)*]

Temporarily suspend ZALTRAP:
- At least 4 weeks prior to elective surgery [*see Warnings and Precautions (5.3)*]
- For recurrent or severe hypertension, until controlled. Upon resumption, permanently reduce the ZALTRAP dose to 2 mg per kg [*see Warnings and Precautions (5.5)*].
- For proteinuria of 2 grams per 24 hours. Resume when proteinuria is less than 2 grams per 24 hours. For recurrent proteinuria, suspend ZALTRAP until proteinuria is less than 2 grams per 24 hours and then permanently reduce the ZALTRAP dose to 2 mg per kg [*see Warnings and Precautions (5.7)*].

For toxicities related to irinotecan, 5-fluorouracil (5-FU), or leucovorin, refer to the current respective prescribing information.

2.3 Preparation for Administration

Inspect vials visually prior to use. ZALTRAP is a clear, colorless to pale yellow solution. Do not use vial if the solution is discolored or cloudy or if the solution contains particles.

Do not re-enter the vial after the initial puncture. Discard any unused portion left in the vial.

Withdraw the prescribed dose of ZALTRAP and dilute in 0.9% sodium chloride solution, USP or 5% dextrose solution for injection, USP to achieve a final concentration of 0.6–8 mg/mL.

Use polyvinyl chloride (PVC) infusion bags containing bis (2-ethylhexyl) phthalate (DEHP) or polyolefin infusion bags.

Store diluted ZALTRAP at 2°–8°C (36°–46°F) for up to 24 hours, or at controlled room temperature 20°–25°C (68°–77°F) for up to 8 hours. Discard any unused portion left in the infusion bag.

2.4 Administration

Administer the diluted ZALTRAP solution as an intravenous infusion over 1 hour through a 0.2 micron polyethersulfone filter. Do not use filters made of polyvinylidene fluoride (PVDF) or nylon.

Do not administer as an intravenous (IV) push or bolus.

Do not combine ZALTRAP with other drugs in the same infusion bag or intravenous line.

Administer ZALTRAP using an infusion set made of one of the following materials:
- PVC containing DEHP
- DEHP free PVC containing trioctyl-trimellitate (TOTM)
- polypropylene
- polyethylene lined PVC
- polyurethane

3 DOSAGE FORMS AND STRENGTHS

ZALTRAP is available as:
- 100 mg per 4 mL (25 mg per mL) solution, single-use vial
- 200 mg per 8 mL (25 mg per mL) solution, single-use vial

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Patients treated with ZALTRAP have an increased risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. In patients with mCRC, bleeding/hemorrhage (all grades) were reported in 38% of patients treated with ZALTRAP/FOLFIRI compared to 19% of patients treated with placebo/FOLFIRI. Grade 3–4 hemorrhagic events, including gastrointestinal hemorrhage, hematuria, and post-procedural hemorrhage, were reported in 3% of patients receiving ZALTRAP/FOLFIRI compared with 1% of patients receiving placebo/FOLFIRI. Severe intracranial hemorrhage and pulmonary hemorrhage/hemoptysis including fatal events have also occurred in patients receiving ZALTRAP.

Monitor patients for signs and symptoms of bleeding. Do not initiate ZALTRAP in patients with severe hemorrhage. Discontinue ZALTRAP in patients who develop severe hemorrhage [*see Dosage and Administration (2.2)*].

5.2 Gastrointestinal Perforation

Gastrointestinal (GI) perforation including fatal GI perforation can occur in patients receiving ZALTRAP. Across three Phase 3 placebo-controlled clinical studies (colorectal, pancreatic, and lung cancer populations), the incidence of GI perforation (all grades) was 0.8% for patients treated with ZALTRAP and 0.3% for patients treated with placebo. Grade 3–4 GI perforation events occurred in 0.8% of patients treated with ZALTRAP and 0.2% of patients treated with placebo.

Monitor patients for signs and symptoms of GI perforation. Discontinue ZALTRAP therapy in patients who experience GI perforation [*see Dosage and Administration (2.2)*].

5.3 Compromised Wound Healing

ZALTRAP impairs wound healing in animal models [*see Nonclinical Toxicology (13.2)*].

Grade 3 compromised wound healing was reported in 2 patients (0.3%) treated with ZALTRAP/FOLFIRI regimen and in none of the patients treated with placebo/FOLFIRI regimen.

Suspend ZALTRAP for at least 4 weeks prior to elective surgery. Do not resume ZALTRAP for at least 4 weeks following major surgery and until the surgical wound is fully healed. For minor surgery such as central venous access port placement, biopsy, and tooth extraction, ZALTRAP may be initiated/resumed once the surgical wound is fully healed. Discontinue ZALTRAP in patients with compromised wound healing [*see Dosage and Administration (2.2)*].

5.4 Fistula Formation

Fistula formation involving gastrointestinal and non-gastrointestinal sites occurs at a higher incidence in patients treated with ZALTRAP. In patients with mCRC, fistulas (anal, enterovesical, enterocutaneous, colovaginal, intestinal sites) were reported in 9 of 611 patients (1.5%) treated with ZALTRAP/FOLFIRI regimen and 3 of 605 patients (0.5%) treated with placebo/FOLFIRI regimen. Grade 3 GI fistula formation occurred in 2 patients treated with ZALTRAP (0.3%) and in 1 placebo-treated patient (0.2%).

Discontinue ZALTRAP therapy in patients who develop fistula [*see Dosage and Administration (2.2)*].

5.5 Hypertension

ZALTRAP increases the risk of Grade 3–4 hypertension. There is no clinical trial experience administering ZALTRAP to patients with NYHA class III or IV heart failure. In patients with mCRC,

Grade 3 hypertension (defined as requiring adjustment in existing anti-hypertensive therapy or treatment with more than one drug) was reported in 1.5% of patients treated with placebo/FOLFIRI and 19% of patients treated with ZALTRAP/FOLFIRI. Grade 4 hypertension (hypertensive crisis) was reported in 1 patient (0.2%) treated with ZALTRAP/FOLFIRI. Among those patients treated with ZALTRAP/FOLFIRI developing Grade 3–4 hypertension, 54% had onset during the first two cycles of treatment.

Monitor blood pressure every two weeks or more frequently as clinically indicated during treatment with ZALTRAP. Treat with appropriate anti-hypertensive therapy and continue monitoring blood pressure regularly. Temporarily suspend ZALTRAP in patients with uncontrolled hypertension until controlled, and permanently reduce ZALTRAP dose to 2 mg per kg for subsequent cycles. Discontinue ZALTRAP in patients with hypertensive crisis or hypertensive encephalopathy [*see Dosage and Administration (2.2)*].

5.6 Arterial Thromboembolic Events

Arterial thromboembolic events (ATE), including transient ischemic attack, cerebrovascular accident, and angina pectoris, occurred more frequently in patients who have received ZALTRAP. In patients with mCRC, ATE was reported in 2.6% of patients treated with ZALTRAP/FOLFIRI and 1.7% of patients treated with placebo/FOLFIRI. Grade 3–4 events occurred in 11 patients (1.8%) treated with ZALTRAP/FOLFIRI and 4 patients (0.7%) treated with placebo/FOLFIRI.

Discontinue ZALTRAP in patients who experience an ATE [*see Dosage and Administration (2.2)*].

5.7 Proteinuria

Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) occurred more frequently in patients treated with ZALTRAP. In patients with mCRC, proteinuria was reported in 62% patients treated with ZALTRAP/FOLFIRI compared to 41% patients treated with placebo/FOLFIRI. Grade 3–4 proteinuria occurred in 8% of patients treated with ZALTRAP/FOLFIRI compared to 1% of patients treated with placebo/FOLFIRI [*see Adverse Reactions (6.1)*]. Nephrotic syndrome occurred in 2 patients (0.5%) treated with ZALTRAP/FOLFIRI compared to none of the patients treated with placebo/FOLFIRI. TMA was reported in 3 of 2258 patients with cancer enrolled across completed studies.

Monitor proteinuria by urine dipstick analysis and/or urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria during ZALTRAP therapy. Patients with a dipstick of ≥2+ for protein or a UPCR greater than 1 should undergo a 24-hour urine collection.

Suspend ZALTRAP administration for proteinuria 2 grams per 24 hours or more, and resume when proteinuria is less than 2 grams per 24 hours. If recurrent, suspend until proteinuria is less than 2 grams per 24 hours and then permanently reduce the ZALTRAP dose to 2 mg per kg. Discontinue ZALTRAP in patients who develop nephrotic syndrome or TMA [*see Dosage and Administration (2.2)*].

5.8 Neutropenia and Neutropenic Complications

A higher incidence of neutropenic complications (febrile neutropenia and neutropenic infection) occurred in patients receiving ZALTRAP. In patients with mCRC, Grade 3–4 neutropenia occurred in 37% of patients treated with ZALTRAP/FOLFIRI compared to 30% patients treated with placebo/FOLFIRI [*see Adverse Reactions (6.1)*]. Grade 3–4 febrile neutropenia occurred in 4% of patients treated with ZALTRAP/FOLFIRI compared to 2% of patients treated with placebo/FOLFIRI. Grade 3–4 neutropenic infection/sepsis occurred in 1.5% of patients treated with ZALTRAP/FOLFIRI and 1.2% of patients treated with placebo/FOLFIRI.

Monitor CBC with differential count at baseline and prior to initiation of each cycle of ZALTRAP. Delay ZALTRAP/FOLFIRI until neutrophil count is at or above 1.5×10^9/L.

5.9 Diarrhea and Dehydration

The incidence of severe diarrhea is increased in patients treated with ZALTRAP/FOLFIRI. In patients with mCRC, Grade 3–4 diarrhea was reported in 19% of patients treated with ZALTRAP/FOLFIRI compared to 8% of patients treated with placebo/FOLFIRI. Grade 3–4 dehydration was reported in 4% of patients treated with ZALTRAP/FOLFIRI compared to 1% of patients treated with placebo/FOLFIRI [*see Adverse Reactions (6.1)*]. The incidence of diarrhea is increased in patients who are age 65 years or older as compared to patients younger than 65 years of age [*see Geriatric Use (8.5)*]. Monitor elderly patients closely for diarrhea.

5.10 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS (also known as posterior reversible encephalopathy syndrome) was reported in 0.5% of 3795 patients treated with ZALTRAP monotherapy or in combination with chemotherapy.

Confirm the diagnosis of RPLS with MRI and discontinue ZALTRAP in patients who develop RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae or death [*see Dosage and Administration (2.2)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hemorrhage [*see Boxed Warning, Warnings and Precautions (5.1)*]
- Gastrointestinal Perforation [*see Boxed Warning, Warnings and Precautions (5.2)*]
- Compromised Wound Healing [*see Boxed Warning, Warnings and Precautions (5.3)*]
- Fistula Formation [*see Warnings and Precautions (5.4)*]
- Hypertension [*see Warnings and Precautions (5.5)*]
- Arterial Thromboembolic Events [*see Warnings and Precautions (5.6)*]
- Proteinuria [*see Warnings and Precautions (5.7)*]
- Neutropenia and Neutropenic Complications [*see Warnings and Precautions (5.8)*]
- Diarrhea and Dehydration [*see Warnings and Precautions (5.9)*]
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [*see Warnings and Precautions (5.10)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under varying designs and in different patient populations, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The safety of ZALTRAP in combination with FOLFIRI was evaluated in 1216 previously treated patients with metastatic colorectal cancer (Study 1) who were treated with ZALTRAP 4 mg per kg intravenous (N=611) or placebo (N=605) every two weeks (one cycle) in a randomized (1:1), double-blind, placebo-controlled Phase 3 study. Patients received a median of 9 cycles of ZALTRAP/FOLFIRI or 8 cycles of placebo/FOLFIRI.

The most common adverse reactions (all grades, ≥20% incidence) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm , in order of decreasing frequency, were leukopenia, diarrhea, neutropenia, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache (see Table 1).

The most common Grade 3–4 adverse reactions (≥5%) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm, in order of decreasing frequency, were neutropenia, diarrhea, hypertension, leukopenia, stomatitis, fatigue, proteinuria, and asthenia (see Table 1).

The most frequent adverse reactions leading to permanent discontinuation in ≥1% of patients treated with ZALTRAP/FOLFIRI regimen were asthenia/fatigue, infections, diarrhea, dehydration,

hypertension, stomatitis, venous thromboembolic events, neutropenia, and proteinuria.

The ZALTRAP dose was reduced and/or omitted in 17% of patients compared to placebo-dose modification in 5% of patients. Cycle delays >7 days occurred in 60% of patients treated with ZALTRAP/FOLFIRI compared with 43% of patients treated with placebo/FOLFIRI.

The most common adverse reactions and laboratory abnormalities during study treatment in Study 1 where the incidence was ≥5% (all grades) in patients receiving ZALTRAP in combination with FOLFIRI and which occurred at ≥2% higher frequency in patients treated with ZALTRAP/FOLFIRI compared to placebo/FOLFIRI are shown in Table 1.

Table 1 – Selected Adverse Reactions and Laboratory Findings in Study 1:

Primary System Organ Class **Preferred Term (%)**	**Placebo/FOLFIRI (N=605)**		**ZALTRAP/FOLFIRI (N=611)**	
	All grades	**Grades 3–4**	**All grades**	**Grades 3–4**
Infections and infestations				
Urinary Tract Infection	6%	0.8%	9%	0.8%
Blood and lymphatic system disorders				
Leukopenia	72%	12%	78%	16%
Neutropenia	57%	30%	67%	37%
Thrombocytopenia	35%	2%	48%	3%
Metabolism and nutrition disorders				
Decreased Appetite	24%	2%	32%	3%
Dehydration	3%	1%	9%	4%
Nervous system disorders				
Headache	9%	0.3%	22%	2%
Vascular disorders				
Hypertension	11%	1.5%	41%	19%
Respiratory, thoracic and mediastinal disorders				
Epistaxis	7%	0	28%	0.2%
Dysphonia	3%	0	25%	0.5%
Dyspnea	9%	0.8%	12%	0.8%
Oropharyngeal Pain	3%	0	8%	0.2%
Rhinorrhea	2%	0	6%	0
Gastrointestinal disorders				
Diarrhea	57%	8%	69%	19%
Stomatitis	33%	5%	50%	13%
Abdominal Pain	24%	2%	27%	4%
Abdominal Pain Upper	8%	1%	11%	1%
Hemorrhoids	2%	0	6%	0
Rectal Hemorrhage	2%	0.5%	5%	0.7%
Proctalgia	2%	0.3%	5%	0.3%
Skin and subcutaneous tissue disorders				
Palmar-Plantar Erythrodysesthesia Syndrome	4%	0.5%	11%	3%
Skin Hyperpigmentation	3%	0	8%	0
Renal and urinary disorders				

Proteinuria*	41%	1%	62%	8%
Serum creatinine increased	19%	0.5%	23%	0
General disorders and administration site conditions				
Fatigue	39%	8%	48%	13%
Asthenia	13%	3%	18%	5%
Investigations				
AST increased	54%	2%	62%	3%
ALT increased	39%	2%	50%	3%
Weight decreased	14%	0.8%	32%	3%

Note: Adverse Reactions are reported using MedDRA version MEDDRA13.1 and graded using NCI CTC version 3.0

* Compilation of clinical and laboratory data

Infections occurred at a higher frequency in patients receiving ZALTRAP/FOLFIRI (46%, all grades; 12%, Grade 3–4) than in patients receiving placebo/FOLFIRI (33%, all grades; 7%, Grade 3–4), including urinary tract infection, nasopharyngitis, upper respiratory tract infection, pneumonia, catheter site infection, and tooth infection.

In patients with mCRC, severe hypersensitivity reactions have been reported with ZALTRAP/FOLFIRI (0.3%) and placebo/FOLFIRI (0.5%).

In patients with mCRC, venous thromboembolic events (VTE), consisting primarily of deep venous thrombosis and pulmonary embolism, occurred in 9% of patients treated with ZALTRAP/FOLFIRI and 7% of patients treated with placebo/FOLFIRI. Grade 3–4 VTE occurred in 8% of patients treated with ZALTRAP/FOLFIRI and in 6% of patients treated with placebo/FOLFIRI. Pulmonary embolism occurred in 5% of patients treated with ZALTRAP/FOLFIRI and 3.4% of patients treated with placebo/FOLFIRI.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In patients with various cancers across 15 studies, 1.4% (41/2862) of patients tested positive for anti-product antibody (APA) at baseline. The incidence of APA development was 3.1% (53/1687) in patients receiving intravenous ziv-aflibercept and 1.7% (19/1134) in patients receiving placebo. Among patients who tested positive for APA and had sufficient samples for further testing, neutralizing antibodies were detected in 17 of 48 ziv-aflibercept-treated patients and in 2 of 40 patients receiving placebo.

The mean free ziv-aflibercept trough concentrations were lower in patients with positive neutralizing antibodies than in the overall population. The impact of neutralizing antibodies on efficacy and safety could not be assessed based on limited available data.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ZALTRAP with the incidence of antibodies to other products may be misleading.

6.3 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ZALTRAP. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Musculoskeletal and connective tissue disorders: Osteonecrosis of the jaw

Cardiac disorders: Cardiac failure, Ejection fraction decreased

7 DRUG INTERACTIONS

No dedicated drug-drug interaction studies have been conducted for ZALTRAP. No clinically important pharmacokinetic drug-drug interactions were found between ziv-aflibercept and irinotecan/SN-38 or 5-FU, based on cross-study comparisons and population pharmacokinetic analyses.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with ZALTRAP in pregnant women. ZALTRAP was embryotoxic and teratogenic in rabbits at exposure levels lower than human exposures at the recommended dose, with increased incidences of external, visceral, and skeletal fetal malformations. ZALTRAP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Ziv-aflibercept produced embryo-fetal toxicity when administered every 3 days during organogenesis in pregnant rabbits at all intravenous doses tested, ≥ 3 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation losses and external (including anasarca, umbilical hernia, diaphragmatic hernia and gastroschisis, cleft palate, ectrodactyly, and atresia), visceral (in the heart, great vessels, and arteries), and skeletal fetal malformations (including fused vertebrae, sternebrae, and ribs; supernumerary arches and ribs, and incomplete ossification). Administration of the 3 mg per kg dose to rabbits resulted in systemic exposure (AUC) that was approximately 30% of the AUC in patients at the recommended dose. The incidence and severity of fetal anomalies increased with increasing dose.

8.3 Nursing Mothers

It is not known whether ZALTRAP is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ZALTRAP, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established. In a dose-escalation, safety, and tolerability study, 21 patients ages 2 to 21 years (median age 12.9) with solid tumors received ZALTRAP at doses ranging from 2 to 3 mg/kg, IV, every two weeks. The pharmacokinetics of free ziv-aflibercept were evaluated in 8 of these patients (ages 5 to 17 years) [*see Clinical Pharmacology (12.3)*]. The maximum tolerated dose in the study was 2.5 mg/kg, below the dose known to be safe and effective in adults with mCRC.

8.5 Geriatric Use

Of the 611 patients with mCRC, patients treated with ZALTRAP/FOLFIRI, 205 (34%) were 65 years or older, and 33 (5%) were 75 years or older. Elderly patients (≥65 years of age) experienced higher incidences (≥5%) of diarrhea, dizziness, asthenia, weight decrease, and dehydration when compared to younger patients. Monitor elderly patients more closely for diarrhea and dehydration [*see Warnings and Precautions (5.9)*].

The effect of ZALTRAP on overall survival was similar in patients <65 years old and ≥65 years old

who received ZALTRAP/FOLFIRI.

No dose adjustment of ZALTRAP is recommended for patients greater than or equal to 65 years of age.

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of ziv-aflibercept.

Based on a population PK analysis with data from 1507 patients, ziv-aflibercept exposure in patients with mild and moderate hepatic impairment were similar to those in patients with normal hepatic function [*see Clinical Pharmacology (12.3)*]. There are no data available for patients with severe hepatic impairment.

8.7 Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of ziv-aflibercept.

Based on a population PK analysis with data from 1507 patients, ziv-aflibercept exposure in patients with mild, moderate, and severe renal impairment were similar to those in patients with normal renal function [*see Clinical Pharmacology (12.3)*].

8.8 Females and Males of Reproductive Potential

Male and female reproductive function and fertility may be compromised during treatment with ZALTRAP, as suggested by findings in monkeys [*see Nonclinical Toxicology (13.1)*]. These animal findings were reversible within 18 weeks after cessation of treatment. Females and males of reproductive potential should use highly effective contraception during and up to a minimum of 3 months after the last dose of treatment.

10 OVERDOSAGE

There have been no cases of overdose reported with ZALTRAP. There is no information on the safety of ZALTRAP given at doses exceeding 7 mg per kg every 2 weeks or 9 mg per kg every 3 weeks.

11 DESCRIPTION

Ziv-aflibercept is a recombinant fusion protein consisting of Vascular Endothelial Growth Factor (VEGF)-binding portions from the extracellular domains of human VEGF Receptors 1 and 2 fused to the Fc portion of the human IgG1. Ziv-aflibercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) K-1 mammalian expression system. Ziv-aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa.

ZALTRAP is a sterile, clear, colorless to pale yellow, non-pyrogenic, preservative-free, solution for administration by intravenous infusion. ZALTRAP is supplied in single-use vials of 100 mg per 4 ml and 200 mg per 8 ml formulated as 25 mg/mL ziv-aflibercept in polysorbate 20 (0.1%), sodium chloride (100 mM), sodium citrate (5 mM), sodium phosphate (5 mM), and sucrose (20%), in Water for Injection USP, at a pH of 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ziv-aflibercept acts as a soluble receptor that binds to human VEGF-A (equilibrium dissociation

constant K_D of 0.5 pM for VEGF-A_{165} and 0.36 pM for VEGF-A_{121}), to human VEGF-B (K_D of 1.92 pM), and to human PlGF (K_D of 39 pM for PlGF-2). By binding to these endogenous ligands, ziv-aflibercept can inhibit the binding and activation of their cognate receptors. This inhibition can result in decreased neovascularization and decreased vascular permeability.

In animals, ziv-aflibercept was shown to inhibit the proliferation of endothelial cells, thereby inhibiting the growth of new blood vessels. Ziv-aflibercept inhibited the growth of xenotransplanted colon tumors in mice.

12.3 Pharmacokinetics

Plasma concentrations of free and VEGF-bound ziv-aflibercept were measured using specific enzyme-linked immunosorbent assays (ELISAs). Free ziv-aflibercept concentrations appear to exhibit linear pharmacokinetics in the dose range of 2–9 mg/kg. Following 4 mg/kg every two weeks intravenous administration of ZALTRAP, the elimination half-life of free ziv-aflibercept was approximately 6 days (range 4–7 days). Steady state concentrations of free ziv-aflibercept were reached by the second dose. The accumulation ratio for free ziv-aflibercept was approximately 1.2 after administration of 4 mg/kg every two weeks.

Specific Populations

Based on a population pharmacokinetic analysis, age, race, and gender did not have a clinically important effect on the exposure of free ziv-aflibercept. Patients weighing ≥100 kg had a 29% increase in systemic exposure compared to patients weighing 50 to 100 kg.

Hepatic impairment

Based on a population pharmacokinetic analysis which included patients with mild (total bilirubin >1.0×–1.5× ULN and any SGOT/AST, n=63) and moderate (total bilirubin >1.5×–3× ULN and any SGOT/AST, n=5) hepatic impairment, there was no effect of total bilirubin, aspartate amino transferase, and alanine amino transferase on the clearance of free ziv-aflibercept. There is no data available for patients with severe hepatic impairment (total bilirubin >3× ULN and any SGOT/AST).

Renal impairment

Based on a population pharmacokinetic analysis which included patients with mild (CL_{CR} 50–80 mL/min, n=549), moderate (CL_{CR} 30–50 mL/min, n=96), and severe renal impairment (CL_{CR} <30 mL/min, n=5), there was no clinically important effect of creatinine clearance on the clearance of free ziv-aflibercept.

Pediatrics

Following intravenous administration of ZALTRAP 2.0 mg/kg, 2.5 mg/kg, or 3.0 mg/kg every two weeks to 8 pediatric patients with solid tumors (ages 5 to 17 years), the mean elimination half-life of free ziv-aflibercept, determined after the first dose, was approximately 4 days (range 3–6 days).

12.6 Cardiac Electrophysiology

The effect of 6 mg/kg intravenous ZALTRAP every three weeks on QTc interval was evaluated in 87 patients with solid tumors in a randomized, placebo-controlled study. No large changes in the mean QT interval from baseline (i.e., greater than 20 ms as corrected for placebo) based on Fridericia correction method were detected in the study. However, a small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded due to limitations of the study design.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate carcinogenicity or mutagenicity of ziv-aflibercept.

Ziv-aflibercept impaired reproductive function and fertility in monkeys. In a 6-month repeat-dose toxicology study in sexually mature monkeys, ziv-aflibercept inhibited ovarian function and follicular development, as evidenced by: decreased ovary weight, decreased amount of luteal tissue, decreased number of maturing follicles, atrophy of uterine endometrium and myometrium, vaginal atrophy, abrogation of progesterone peaks and menstrual bleeding. Alterations in sperm morphology and decreased sperm motility were noted in male monkeys. These effects were observed at all doses tested including the lowest dose tested, 3 mg per kg. Reversibility was observed within 18 weeks after cessation of treatment. Systemic exposure (AUC) with a 3 mg per kg per dose in monkeys was approximately 60% of the AUC in patients at the recommended dose.

13.2 Animal Toxicology and/or Pharmacology

Weekly/every two weeks intravenous administration of ziv-aflibercept to growing young adult (sexually mature) cynomolgus monkeys for up to 6 months resulted in changes in the bone (effects on growth plate and the axial and appendicular skeleton), nasal cavity (atrophy/loss of the septum and/or turbinates), kidney (glomerulopathy with inflammation), ovary (decreased number of maturing follicles, granulosa cells, and/or theca cells), and adrenal gland (decreased vacuolation with inflammation). Most ziv-aflibercept-related findings were noted from the lowest dose tested (3 mg per kg per dose) correlating to 60% of the AUC at the human recommended dose.

In another study in sexually immature cynomolgus monkeys (treated intravenous for 3 months), similar effects were observed. The skeletal and nasal cavity effects were not reversible after a post-dosing recovery period.

Repeated administration of ziv-aflibercept resulted in a delay in wound healing in rabbits. In full-thickness excisional and incisional skin wound models, ziv-aflibercept administration reduced fibrous response, neovascularization, epidermal hyperplasia/re-epithelialization, and tensile strength.

14 CLINICAL STUDIES

Study 1 was a randomized, double-blind, placebo-controlled study in patients with metastatic colorectal cancer (mCRC) who are resistant to or have progressed during or within 6 months of receiving oxaliplatin-based combination chemotherapy, with or without prior bevacizumab. A total of 1226 patients were randomized (1:1) to receive either ZALTRAP (N=612; 4 mg per kg as a 1 hour intravenous infusion on day 1) or placebo (N=614), in combination with 5-fluorouracil plus irinotecan [FOLFIRI: irinotecan 180 mg per m^2 IV infusion over 90 minutes and leucovorin (dl racemic) 400 mg per m² intravenous infusion over 2 hours at the same time on day 1 using a Y-line, followed by 5-FU 400 mg per m² intravenous bolus, followed by 5-FU 2400 mg per m² continuous intravenous infusion over 46-hours]. The treatment cycles on both arms were repeated every 2 weeks. Patients were treated until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall survival. Treatment assignment was stratified by the ECOG performance status (0 versus 1 versus 2) and according to prior therapy with bevacizumab (yes or no).

Demographics characteristics were similar between treatment arms. Of the 1226 patients randomized, the median age was 61 years, 59% were men, 87% were White, 7% were Asian, 3.5% were Black, and 98% had a baseline ECOG performance status (PS) of 0 or 1. Among the 1226 randomized patients, 89% and 90% of patients treated with placebo/FOLFIRI and ZALTRAP/FOLFIRI, respectively, received prior oxaliplatin-based combination chemotherapy in the metastatic/advanced setting. A total of 346 patients (28%) received bevacizumab in combination with the prior oxaliplatin-based treatment.

Overall efficacy results for the ZALTRAP/FOLFIRI regimen versus the placebo/FOLFIRI regimen are summarized in Figure 1 and Table 2.

Figure 1 – Overall survival (months) – Kaplan-Meier curves by treatment group

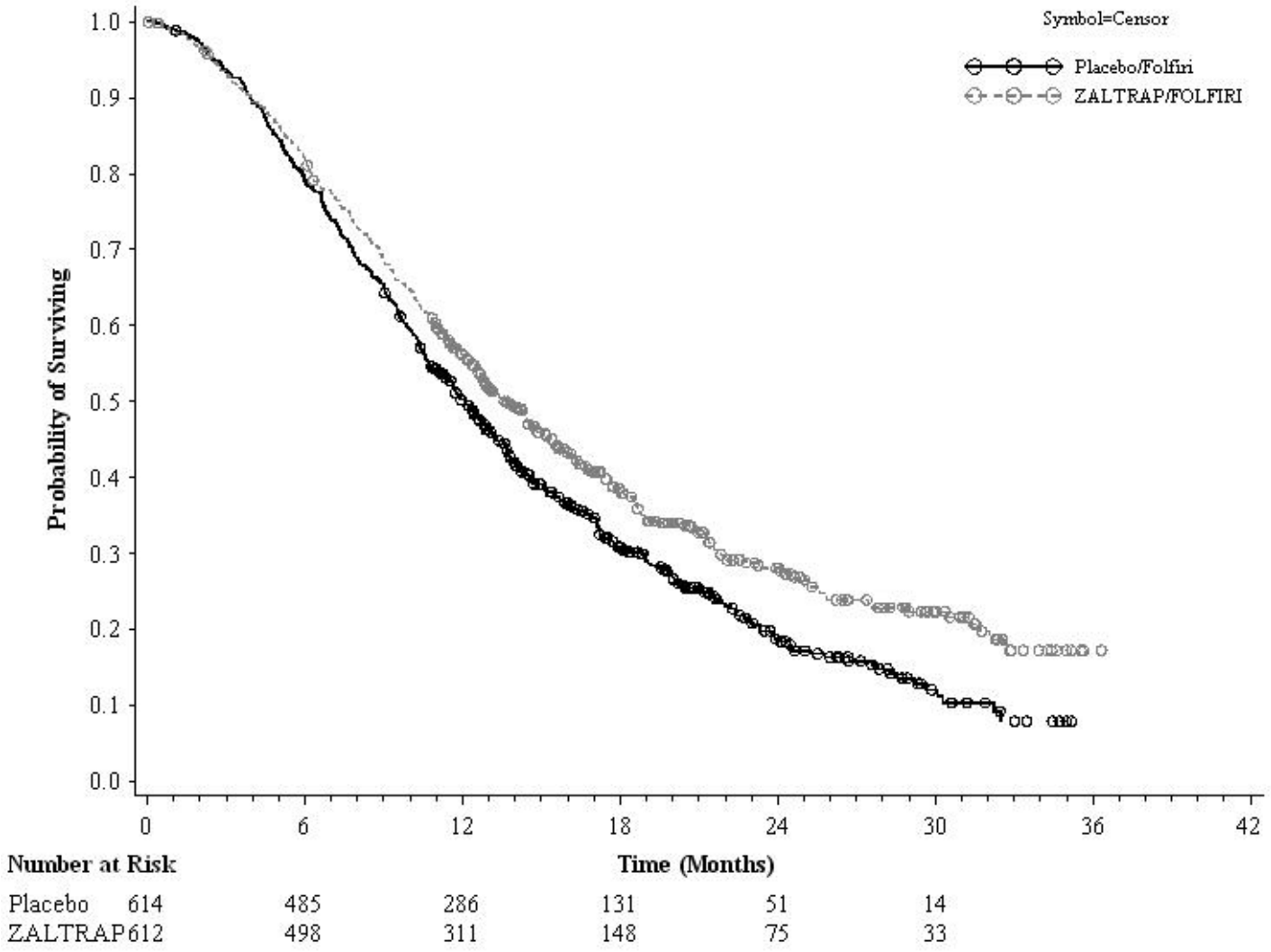

Table 2 Main efficacy outcome measures*

	Placebo/FOLFIRI (N=614)	ZALTRAP/FOLFIRI (N=612)
Overall Survival		
Number of deaths, n (%)	460 (74.9%)	403 (65.8%)
Median overall survival (95% CI) (months)	12.06 (11.07 to 13.08)	13.50 (12.52 to 14.95)
Stratified Hazard ratio (95% CI)	0.817 (0.714 to 0.935)	
Stratified Log-Rank test p-value	0.0032	
Progression Free Survival (PFS)*		
Number of events, n (%)	454 (73.9%)	393 (64.2%)
Median PFS (95% CI) (months)	4.67 (4.21 to 5.36)	6.90 (6.51 to 7.20)
Stratified Hazard ratio (95% CI)	0.758 (0.661 to 0.869)	
Stratified Log-Rank test p-value †	0.00007	
Overall Response Rate (CR+PR) (95% CI) (%)‡	11.1 (8.5 to 13.8)	19.8 (16.4 to 23.2)
Stratified Cochran-Mantel-Haenszel test p-value	0.0001	

* PFS (based on tumor assessment by the IRC): Significance threshold is set to 0.0001.

† Stratified on ECOG Performance Status (0 vs 1 vs 2) and Prior Bevacizumab (yes vs no)

‡ Overall objective response rate by IRC

Planned subgroup analyses for overall survival based on stratification factors at randomization yielded

an HR of 0.86 (95% CI: 0.68 to 1.1) in patients who received prior bevacizumab and an HR of 0.79 (95% CI: 0.67 to 0.93) in patients without prior bevacizumab exposure.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZALTRAP is supplied in 5 mL and 10 mL vials containing ziv-aflibercept at a concentration of 25 mg/mL.

NDC 0024-5840-01: carton containing one (1) single-use vial of 100 mg per 4mL (25 mg/mL)

NDC 0024-5840-03: carton containing three (3) single-use vials of 100 mg per 4 mL (25 mg/mL)

NDC 0024-5841-01: carton containing one (1) single-use vial of 200 mg per 8 mL (25 mg/mL)

16.2 Storage and Handling

Store ZALTRAP vials in a refrigerator at 2 to 8°C (36 to 46°F). Keep the vials in the original outer carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- That ZALTRAP can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.
- That ZALTRAP increases the risk of compromised wound healing. Instruct patients not to undergo surgery or procedures (including tooth extractions) without discussing first with their health care provider.
- That ZALTRAP can cause or exacerbate existing hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.
- To notify the health care provider of severe diarrhea, vomiting, or severe abdominal pain.
- To notify their health care provider of fever or other signs of infection.
- Of an increased risk of arterial thromboembolic events.
- Of the potential risks to the fetus or neonate using ZALTRAP during pregnancy or nursing and of the need to use highly effective contraception in both males and females during and for at least 3 months following last dose of ZALTRAP therapy. Advise the patient to immediately contact the healthcare provider if they or their partner becomes pregnant during treatment with ZALTRAP.

Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY
U.S. License # 1752

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Revision Date 6/2016

PRINCIPAL DISPLAY PANEL - 100 mg/4 mL Vial Carton

NDC 0024-5840-01

ZALTRAP®
(ziv-aflibercept)
Injection for
Intravenous Infusion

100 mg/4 mL
(25 mg/mL)

For intravenous infusion only.
Not to be administered by
other routes.
Hyperosmotic, must be diluted.

Single-use vial.
Discard unused portion

Rx ONLY

SANOFI

PRINCIPAL DISPLAY PANEL - 200 mg/8 mL Vial Carton

NDC 0024-5841-01

ZALTRAP®
(ziv-aflibercept)
Injection for
Intravenous Infusion

200 mg/8 mL
(25 mg/mL)

For intravenous infusion only.
Not to be administered by
other routes.
Hyperosmotic, must be diluted.

Single-use vial.
Discard unused portion

Rx ONLY

SANOFI

ZALTRAP

ziv-aflibercept solution, concentrate

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0024-5840
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
aflibercept (UNII: 15C2VL427D) (aflibercept - UNII:15C2VL427D)	aflibercept	100 mg in 4 mL

Inactive Ingredients	
Ingredient Name	**Strength**
sucrose (UNII: C151H8M554)	
sodium chloride (UNII: 451W47IQ8X)	
trisodium citrate dihydrate (UNII: B22547B95K)	
citric acid monohydrate (UNII: 2968PHW8QP)	
polysorbate 20 (UNII: 7T1F30V5YH)	
sodium phosphate, dibasic, heptahydrate (UNII: 70WT22SF4B)	
sodium phosphate, monobasic, monohydrate (UNII: 593YOG76RN)	
sodium hydroxide (UNII: 55X04QC32I)	
hydrochloric acid (UNII: QTT17582CB)	
water (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0024-5840-01	1 in 1 CARTON	08/03/2012	
1		4 mL in 1 VIAL; Type 0: Not a Combination Product		
2	NDC:0024-5840-03	3 in 1 CARTON	08/03/2012	
2		4 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125418	08/03/2012	

ZALTRAP

ziv-aflibercept solution, concentrate

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0024-5841
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
aflibercept (UNII: 15C2VL427D) (aflibercept - UNII:15C2VL427D)	aflibercept	200 mg in 8 mL

Inactive Ingredients	
Ingredient Name	Strength
sucrose (UNII: C151H8M554)	
sodium chloride (UNII: 451W47IQ8X)	
trisodium citrate dihydrate (UNII: B22547B95K)	
citric acid monohydrate (UNII: 2968PHW8QP)	
polysorbate 20 (UNII: 7T1F30V5YH)	
sodium phosphate, dibasic, heptahydrate (UNII: 70WT22SF4B)	
sodium phosphate, monobasic, monohydrate (UNII: 593YOG76RN)	
sodium hydroxide (UNII: 55X04QC32I)	
hydrochloric acid (UNII: QTT17582CB)	
water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0024-5841-01	1 in 1 CARTON	08/03/2012	
1		8 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125418	08/03/2012	

Labeler - sanofi-aventis U.S. LLC (824676584)

Establishment

Name	Address	ID/FEI	Business Operations
sanofi-aventis Deutschland GmbH		313218430	MANUFACTURE(0024-5840, 0024-5841) , ANALYSIS(0024-5840, 0024-5841) , API MANUFACTURE(0024-5840, 0024-5841) , LABEL(0024-5840, 0024-5841) , PACK(0024-5840, 0024-5841)

Revised: 6/2016 sanofi-aventis U.S. LLC